EXHIBIT B

MEDLINE(R)

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Renal insufficiency induced by cisplatin in rats is ameliorated by cyclosporin A.

Campbell P I; al-Nasser I A
Department of Biochemistry, College of Science, King Saud University, Riyadh, Saudi-Arabia.
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Cyclosporin A (CsA) is a potent inhibitor of the Ca(2+)-dependent "pore" in isolated mitochondrial from diverse sources. Cisplatin-induced acute renal failure has been associated with morphological and functional alterations in renal cortex mitochondrial (RCM). This study was undertaken to examine the probable involvement of Ca(2+)-dependent permeabilization of RCM in cisplatin nephrotoxicity. RCM from rats injected with cisplatin (5 mg/kg body wt) 4 days earlier showed a significantly reduced capacity of retaining matrix Ca2+ and membrane potential in the presence of 15 nmol Ca2+/mg protein and 0.1 mM Pi (inorganic phosphate), compared to controls (those of rats that received carrier alone). These indices of mitochondrial dysfunction were restored to control levels when 1 microM CsA was added to assay media of RCM obtained from cisplatin-treated rats. Renal insufficiency induced by cisplatin assessed by serum creatinine and urea levels was significantly alleviated in rats 4 days after i.p. injections of cisplatin (5 mg/kg body wt) and CsA (50 micrograms/kg body wt), compared to those injected with cisplatin alone. Our findings support an involvement of Ca(2+)-mediated RCM damage in the mechanism of cisplatin nephrotoxicity, and suggest that suitable antagonists of Ca(2+)-dependent "pore" formation may improve renal tolerance to cisplatin.

EXHIBIT B, CONTINUED

Biosis Previews(R)

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Prevention of adriamycin aglycone-induced changes of inner mitochondrial membrane permeability by cyclosporin A

Author: Al-Nasser Ibrahim A
Author Address: Dep. Biochem., Coll. Sci., King Saud Univ., PO Box 2455, Riyadh 11451, Saudi Arabia**Saudi Arabia
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Abstract: The effect of adriamycin aglycone (7-hydroxy aglycone) on the permeability of inner mitochondrial membrane was examined. Tetraphenyl phosphonium ion (TPP+) uptake, estimated with a TPP+-sensitive electrode, was used to monitor changes in isolated heart or liver inner mitochondrial membrane potential. Isolated heart and liver mitochondria were able to accumulate and retain TPP+ after energisation with succinate. Addition of adriamycin aglycone (10-150 mu-m for heart samples or 50-350 mu-m for liver), to the mitochondria led to a loss of the ability of mitochondria to retain TPP+. The latter is an indication of loss of membrane potential. Addition of 1 mu-m cyclosporin A (CsA) prior to the addition of succinate abolished the effect of adriamycin aglycone on TPP+ retention. There is ample evidence that adriamycin-induced cardiotoxicity is related to changes in morphology and/or function of mitochondria. The results of this study suggest that adriamycin aglycone induced opening of inner mitochondrial membrane pore which led to the dissipation of membrane potential. The effect of adriamycin aglycone was blocked by CsA, and thus restored the membrane potential. These results indicate that CsA may be useful as a protective agent against the toxicity of adriamycin derivatives.